2007 WL 2745815 (Bd.Pat.App. & Interf.)

Board of Patent Appeals and Interferences

Patent and Trademark Office (P.T.O.)

***1** EX PARTE
BUCHI
REDDY REGURI AND SUDHAKAR SUNKARI

Decided: September 6, 2007

Before TONI R. SCHEINER, ERIC GRIMES, and NANCY J. LINCK
Administrative Patent Judges
Opinion by GRIMES
Administrative Patent Judge

Concurring and dissenting opinion by LINCK
Administrative Patent Judge

DECISION ON APPEAL

This is an appeal under 35 U.S.C. § 134 involving claims to specific crystal forms of valsartan. The Examiner has rejected the claims as nonenabled, indefinite, anticipated, and obvious. We have jurisdiction under 35 U.S.C. § 6(b). We reverse all of the rejections.

BACKGROUND

Valsartan is a known compound (Specification ¶ 4) that "is used in the treatment of cardiovascular complaints such as hypertension and heart failure" (*id.*, ¶ 3). The Specification describes "crystalline Form-I and Form-II of Valsartan" (*id.*, ¶ 8).

The disclosed process for preparing Form I crystalline valsartan comprises "a) dissolving Valsartan in a C4-C6 straight or branched chain ketone solvent at 60 - 65°C; b) adding an aliphatic hydrocarbon solvent accompanied by cooling; c) isolating and drying the product of step (b) to obtain crystalline Form-I of Valsartan" (*id.* at ¶¶ 18-21). In a working example, Form I crystalline valsartan is made by dissolving valsartan in methyl isobutyl ketone and precipitating with hexane (*id.* at ¶ 56).

The disclosed process for preparing Form II crystalline Valsartan comprises "(i) dissolving Valsartan in a C4-C6 ketone solvent at 50-55°C temperature; ii) adding an aliphatic hydrocarbon solvent accompanied by cooling; iii) isolating and drying

the product of step (ii) to obtain crystalline Form-II of Valsartan" (*id.* at ¶¶ 32-35). In a working example, Form II crystalline Valsartan is made by dissolving valsartan in methyl propyl ketone and precipitating with hexane (*id.* at ¶ 57).

The Specification provides X-ray diffraction patterns for Form I and Form II crystalline valsartan (Figures 1 and 3, respectively), as well as the X-ray diffraction pattern for "crude Valsartan, which was recrystallised in dichloromethane followed by ethyl acetate …, which is having an amorphous pattern by its X-ray diffractogram" (*id.* at ¶ 55 and Figure 5).

DISCUSSION

1. CLAIMS

Claims 1-12, 30-32, 36-39, and 48 are on appeal. Claims 13-29, 33, and 40-47 are also pending but have been withdrawn from consideration by the Examiner.

***2** Claims 1 and 7 are representative and read as follows:

1. A crystalline Form-I of (S)-N-(1-carboxy-2-methyl-prop-1-yl)-N-pentanoyl-N-[2'-(1H-tetrazol-5-yl)-biphenyl-4-yl methyl] amine.

7. A crystalline Form-II of (S)-N-(1-carboxy-2-methyl-prop-1-yl)-N-pentanoyl-N-[2'-(1H-tetrazol-5-yl)-biphenyl-4-yl methyl] amine.

Claims 1 and 7 are respectively directed to Form I and Form II crystalline Valsartan (cf. Specification, ¶ 2).

2. PRIOR ART

The Examiner relies on the following reference:

Bühlmayer	US 5,399,578	Mar. 21, 1995

3. ENABLEMENT

Claims 1-12, 30-32, 36-39, and 48 stand rejected under 35 U.S.C. § 112, first paragraph, on the basis that "the specification, while being enabling for a crystalline Form-I of valsartan having an x-ray pow[d]er diffraction peak at 2 e value of 5.415, does not reasonably provide enablement for a crystalline Form-I of valsartan having an x-ray pow[d]er diffraction peak at 2 e value of 40" (Answer 4.)

Appellants argue that the

> invention relates to only two specific crystalline forms of the single previously known compound, valsartan. These specific crystalline forms have well-defined X-ray diffraction patterns and thermal properties, which have been provided in the specification. A process for preparing each crystalline form has been described, and a working example was provided for preparing each of the forms. … There is no lack of enablement, and this rejection should be reversed.

(Br. 5.)

We agree with Appellants. The Examiner's concern, as best we understand it, seems to be that some of the claims do not expressly recite the X-ray diffraction peaks that are characteristic of Form I crystalline valsartan. Thus, according to the Examiner's apparent theory, claim 1 encompasses a "Form I valsartan" with a X-ray diffraction peak with a 2 value of, for example, 40, rather than the peaks shown in Figure 1.

The problem with the theory apparently underlying the Examiner's rejection is that a form of crystalline valsartan with a X-ray diffraction peak with a 2 > value of 40 would not be Form I crystalline valsartan. Claims must be interpreted in light of the Specification. *See In re Morris*, 127 F.3d 1048, 1054 (Fed. Cir. 1997). Here, the Specification states that the "Crystalline Form-I of Valsartan has X-ray powder diffraction pattern essentially as shown in [] Table-1" (Specification ¶ 26). Table 1 does not show any X-ray diffraction peaks with a 2 value of 40. Thus, the embodiment asserted by the Examiner to be nonenabled is not within the scope of the claims. The rejection for nonenablement is reversed.

4. DEFINITENESS

Claims 3, 5, 9, and 11 stand rejected under 35 U.S.C. § 112, first paragraph, as indefinite because they refer to Figures 1, 2, 3, and 4, respectively: "Claims must stand alone to define invention, and incorporation into claims by express reference to specification is not permitted. … In order to obviate the rejection, the XRD data or the DSC data of Fig. 1, 2, 3, or 4 must be inserted into the claims." (Answer 6.)

***3** Appellants argue that the Examiner's reliance on *Ex parte Fressola*, 27 USPQ2d 1608 (BPAI 1993), is misplaced (Br. 5). Appellants argue that, unlike the present case, the claim in *Fressola* was a so-called "omnibus claim" (a "system … as disclosed in the specification and drawings herein") (*id.*). Appellants also argue that the present case falls into the exception permitted under *Fressola*, in that "there is no conceivable manner of reducing an X-ray diffraction pattern or differential scanning calorimetry curve into words, and inserting the entire pattern or curve into a claim will not be practical" (*id.* at 6).

We agree with Appellants that the reference to figures in claims 3, 5, 9, and 11 does not render them indefinite. "Incorporation into the claims by express reference to the specification and/or drawings is not permitted except in very limited circumstances." *Fressola*, 27 USPQ2d at 1609. Such incorporation is permitted, however, "where there is no practical way to define the invention in words and where it is more concise to incorporate by reference than duplicating a drawing or table into the claim." *Id.*

The circumstances of this case fall squarely within the exception defined in *Fressola*: there is no practical way to define in words the patterns and curves shown in the figures, and it is more concise to incorporate by reference than to duplicate the figures in the claims. The rejection of claims 3, 5, 9, and 11 for indefiniteness is reversed.

5. ANTICIPATION

Claims 1-12, 30-32, 36-39, and 48 stand rejected under 35 U.S.C. § 102(b) as anticipated by Bühlmayer. The Examiner reasons that Bühlmayer discloses valsartan in crystalline form and therefore anticipates the instant claims (Answer 10). See also *id.* at 8:

> Buhlmayer et al. … does not provide applicants' instant X-ray diffraction data. However, Buhlmayer et al. do name a crystalline form of valsartan …, which puts this product in the public domain. As these forms differ from the claims in that the references are [sic] silent on the X-ray diffraction data, applicants must show that their crystalline forms really are different.

Appellants argue that the process described in Bühlmayer for making valsartan is different from the processes described

in the instant Specification for making Form I and Form II valsartan, and the melting point range disclosed by Bühlmayer is different from the melting point ranges of Form I and Form II valsartan disclosed in the instant Specification (Br. 7). Appellants conclude that Bühlmayer "did not provide any X-ray diffraction or differential scanning calorimetry information, and there is no reason to expect that their crystalline form, prepared by a different process and having a different melting point, would have these properties corresponding to the presently claimed forms of the compound" (*id.*)

***4** We agree with Appellants that the evidence relied on by the Examiner is inadequate to justify shifting the burden of proof to Appellants. When the inherent properties of a prior art product are at issue, "the examiner must provide some evidence or scientific reasoning to establish the reasonableness of the examiner's belief that the functional limitation is an inherent characteristic of the prior art" before the burden is shifted to the applicant to disprove the inherency. *Ex parte Skinner*, 2 USPQ2d 1788, 1789 (BPAI 1986). *See also In re Spada*, 911 F.2d 705, 708 (Fed. Cir. 1990) ("[W]hen the PTO shows *sound basis* for believing that the products of the applicant and the prior art are the same, the applicant has the burden of showing that they are not." (emphasis added)).

Here, it is true that Bühlmayer discloses valsartan "in crystalline form" (Bühlmayer, col. 49, ll. 35-51). The instant claims, however, are limited to only Form I and Form II crystalline valsartan.

The instant Specification states that Form I and Form II crystalline valsartan are made by dissolving valsartan in a ketone solvent and precipitating with an aliphatic hydrocarbon. Bühlmayer obtains valsartan by extraction from aqueous solution with ethyl acetate and crystallization in ethyl acetate (an ester, not a ketone or hydrocarbon).

The instant Specification also discloses that Form I valsartan has a melting point range of 80-91°C, while Form II valsartan has a melting point range of 91-102°C (Specification at ¶¶ 30, 44). Bühlmayer discloses that its crystalline valsartan has a melting point range of "105°C - 1150°C [sic, presumably 105°C - 115°C]" (Bühlmayer, col. 49, ll. 50-51).

Thus, the evidence of record shows that the prior art product was made by a different method and has different physical properties than the claimed Form I and Form II crystalline valsartan. The evidence does not support the Examiner's conclusion that it is reasonable to expect the prior art product to contain either of the claimed crystalline forms of valsartan. We therefore reverse the rejection under 35 U.S.C. § 102(b).

6. OBVIOUSNESS

Claims 1-12, 30-32, 36-39, and 48 stand rejected under 35 U.S.C. § 103 as obvious in view of Bühlmayer and Cheronis. The Examiner relies on Bühlmayer's disclosure of crystalline valsartan and cites Cheronis as teaching that the "skill of art for preparing a compound in a crystalline form by choosing proper solvent (i.e., acetone, ethyl acetate, etc.), temperature, and concentration has been taught" (Answer 12-13). The Examiner concludes that the "employment of a conventional obvious modification of a known process to obtain a pure form (i.e., crystalline or amorphous form) is considered prima facie obvious in the absence of unexpected results" (*id.* at 13).

***5** Appellants argue that the cases cited by the Examiner as supporting the obviousness rejection are distinguishable or are no longer good law, and that Bühlmayer does not "provide a reasonable expectation of success for making a different polymorph, let alone the two specific polymorphs that are being claimed by appellants" (Br. 8-10).

We agree with Appellants that the cited references do not support a prima facie case of obviousness. Bühlmayer is discussed above. As we understand it, the Examiner relies on Cheronis for its teaching of recrystallization methods, and concludes that it would have been obvious to those skilled in the art to recrystallize Bühlmayer's valsartan and thereby obtain the claimed crystalline forms.

We do not agree with the Examiner's conclusion. Cheronis shows that recrystallization was a well-known purification technique in organic chemistry. Thus, those skilled in the art would have considered it obvious to further purify Bühlmayer's valsartan by recrystallization. That would not necessarily lead to the claimed crystalline forms, however. The instant Specification states that Form I and Form II valsartan are obtained by dissolving valsartan in a ketone solvent and adding an aliphatic hydrocarbon solvent to precipitate it.

The only ketone solvent disclosed by Cheronis is acetone, which is said to be "[o]f limited use as a single solvent; more useful as a pair with alcohols" (Cheronis 33, Table 5-1). Cheronis states that hydrocarbons, including hexane, are "[u]seful for many compounds. May be employed with benzene and toluene to form solvent pairs" (*id.*). Cheronis does not disclose that a ketone/hydrocarbon solvent pair was commonly used for recrystallization. Thus, we cannot agree with the Examiner that Cheronis would have led those skilled in the art to the recrystallization conditions that are disclosed in the Specification to be necessary for formation of Form I and Form II crystalline valsartan.

The Examiner has not adequately shown that the cited references would have led those skilled in the art to the conditions needed to make the claimed crystalline forms of valsartan. The rejection under 35 U.S.C. § 103 is reversed.

SUMMARY

We reverse the rejections under 35 U.S.C. § 112, first and second paragraphs, because the Examiner has not established that the claims are not enabled throughout their scope or that they are indefinite. We reverse the rejections under 35 U.S.C. §§ 102(b) and 103 because the Examiner has not shown an adequate basis for concluding that the claimed crystalline forms of valsartan were disclosed in or would have been obvious from the prior art.

REVERSED

CONCURRING AND DISSENTING OPINION

***6** LINCK
Administrative Patent Judge

I concur in the reversal of the rejections under 35 U.S.C. § 112. However, I respectfully dissent with respect to the rejection under 35 U.S.C. § 102(b). The Examiner's prima facie case of anticipation should be affirmed.

Appellants are claiming a prior art compound,
(S)-N-(1-carboxy-2-methyl-prop-1-yl)-N-pentanoyl-N-[2'-(1H-tetrazol-5-yl)-biphenyl-4-yl methyl] amine ("valsartan"[FN1]). *See* Bühlmayer, col. 49 (Example 54) disclosing a "crystalline form" of this compound. The alleged distinguishing characteristic is in the form of the crystals, with Appellants claiming their "Form I" and "Form II" are novel (*see, e.g.*, Specification at 1-2 & claims 1 & 7). They provide very little evidence to show their Forms I and II are different than the Bühlmayer's crystalline form, as they have not provided any comparative physical data for Bühlmayer's compound. One must ask *why* Appellants did not obtain an X-ray powder diffraction pattern or a DSC thermogram for Bühlmayer's crystalline compound. I must assume the results of such a comparison would not support their case.

According to the majority, such data are not needed, since the "evidence relied on by the Examiner is inadequate to justify shifting the burden of proof to Appellants" (*supra* at 6). I disagree. At this point, Appellants should bear the burden to show they are not claiming something that is already in the prior art. *See, e.g., In re Spada,* 911 F.2d 705, 708, 15 USPQ2d 1655, 1658 (Fed. Cir. 1990) ("when the PTO shows a sound basis for believing that the products of the applicant and the prior art are the same, the applicant has the burden of showing that they are not").

The crystalline compound disclosed by Bühlmayer has the *same* chemical formula as that Appellants are trying to claim.

And it's in crystalline form.[FN2] It's also useful for exactly the *same* purpose as that disclosed by Appellants, i.e., to inhibit the action of angiotensin II on its receptors (*e.g.*, Specification 1; Bühlmayer, col. 6, ll. 30-33).

In my view, there is insufficient evidence to suggest that Bühlmayer's *crystalline* form is different than Appellants' Forms I and II. The difference in melting points, relied upon by the majority (see supra p. 7), is not convincing. As one skilled in the art would have known, small differences in melting points provide scant information and should be viewed critically. This is particularly true when, like here, there is no evidence they were obtained under the same conditions, such as rate of heating and sample size, or even method (for example, DSC versus capillary tube). Further, melting points are notoriously sensitive to impurities. In this case, the purity of Appellants' crystals varies, exhibiting a range of color from "white to off-white." (Specification 4-5, ¶¶ 0030 & 0044.) Such impurities could explain, or at least partially explain, their lower melting point.

***7** The majority also relies on differences between how the products were isolated (*see supra* p. 7). Appellants prepared their products by dissolving valsartan in a ketone and adding an aliphatic hydrocarbon to precipitate the compound (Specification 2-3), while Bühlmayer used ethyl acetate (Bühlmayer, col. 49, ll. 50-51). Without more, those skilled in the art would not have concluded different crystallization solvents and systems necessarily yield different crystalline forms.

In fact, such a conclusion is counter to Appellants' own teachings that *any* C4-C6 straight or branched chain ketone solvent and *any* aliphatic hydrocarbon will suffice (Specification 2, ¶¶ 0009-0010). If the crystal structure is as sensitive to the crystallization solvent system as suggested, one would expect more precise teachings regarding that system.

Another concern is that Appellants do not use "consisting of" or even "consisting essentially of" language to exclude valsartan in other forms. Thus, their claims include mixtures of crystals, as long as a crystal of the claimed form is present. It follows that, even if only a trace amount of Bühlmayer's crystalline compound is in crystalline Form I or II, Appellants' claims to these forms would be anticipated. *See Smithkline Beecham Corp. v. Apotex,* 403 F.3d 1331, 1339-40, 74 USPQ2d 1398, 1403-04 (Fed. Cir. 2005) (holding that a claim to "Crystalline paroxetine hydrochloride hemihydrate," in essence, would cover a single molecule of hemihydrate).

It is the Office's responsibility to prevent the issuance of invalid patents. Yet the Office does not have the facilities to determine what form or admixtures of forms Bühlmayer's crystalline compound takes. Given the facts of this case, I conclude the Examiner has made a prima facie case of anticipation under 35 U.S.C. § 102.

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FN1. Valsartan is a commercial product sold by Novartis under the trade name Diovan (approved by the FDA in 2001).

FN2. While Appellants describe a "Reference Example," that example is clearly not Bühlmayer's, as it is "amorphous" (Spec. 8) rather than "crystalline" (Bühlmayer, col. 49, l. 51). Notably, Appellants do not disclose a melting point for their "Reference Example."